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VOLUME VII NUMBER 2

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CLINICAL PROCEEDINGS

OF THE CHILDRENS HOSPITAL

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CONTENTS

MUMPS MENINGOENCEPHALITIS. *David H. Riege, M.D.; Martin H. Smith, M.D., and Lawrence Kilham, M.D.*... 29

ERYTHEMA BULLOSUM MALIGNANS-PLURIORIFICIAL TYPE (STEVENS-JOHNSON DISEASE) REPORT OF A CASE TREATED WITH CORTISONE. *Harold T. Yates, M.D.; Crenshaw D. Briggs, M.D.; William A. Anderson, M.D.; Fernando R. Leyva, M.D. and Ellery Michaud, M.D.*.... 37

SACROCOCCYGEAL TERATOMA. *Harold H. Hawfield, M.D. and William W. Orr, M.D.*..... 50

CLINICO-PATHOLOGICAL CONFERENCE. *Sanford Leikin, M.D., and John A. Washington, M.D.*..... 55

INTRAMUSCULAR ADMINISTRATION OF CHLORAMPHENICOL. A PRELIMINARY NOTE. *Sidney Ross, M.D.; Warren G. Priesser, M.D.; William W. Orr, M.D.; Frederic G. Burke, M.D. and E. Clarence Rice, M.D.*..... 61

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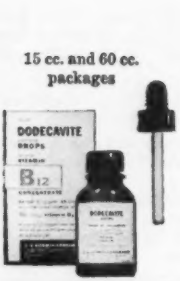

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MUMPS MENINGOENCEPHALITIS

Special Report No. 195

David H. Riege, M.D.
Martin H. Smith, M.D.

Between January 1948 and August 1950 there were twenty-five cases of mumps meningoencephalitis diagnosed at Children's Hospital. The literature is voluminous on the subject of central nervous system involvement in mumps. It is the purpose of this paper to survey the literature and analyze the material contained in this series of cases. We feel this is worthwhile because these cases enable us to bring out certain features of the disease that have not received sufficient emphasis.

The French did most of the original reporting of cases of encephalitis associated with infectious parotitis. Monod[1] in 1902 was the first to make a systematic study from the point of view of determining the presence of increased cells in the spinal fluids of cases other than those with frank central nervous system symptoms. He found the cell count to be abnormal in six out of eight such cases. Maximovitsch[2] in 1880 was the first to describe the pathology in this disease.

Many theories have been advanced regarding the etiology of the central nervous system involvement.[3] The two more tenable theories at present are: first, that the disease is due to involvement of the central nervous system by the primary disease virus; and second, that in the severe cases, at least, an unknown latent neurotropic virus is activated by the primary disease virus.[4] In support of the first or primary virus disease theory are the following facts: the mumps virus has been isolated from the spinal fluid and from the saliva of patients without apparent parotitis;[5,6] no other virus has been so isolated, and in many cases the meningoencephalitic symptoms have preceded or occurred without parotid swelling. In 1934 Montgomery[3] made the statement that the conception of meningoencephalitis as a complication of mumps is probably erroneous and that the infection is apparently due to a virus which has a predilection for the salivary glands, the meninges, the encephalon, the pancreas, and the mature gonads. The determining factor in the localization of the virus is not clear.

The incidence of central nervous system involvement[7] has been noted to vary greatly from epidemic to epidemic ranging from 0.24 per cent in Boston in 1933 to 10 per cent of 1,700 French troops with mumps in 1910. Statistics concerned with the incidence will, of course, vary directly with the intensity of the search for and the reporting of neurological involvement in mumps.

The pathology of mumps meningoencephalitis was well reviewed and described by Donahue[8] in 1941. The brain and cord may show only congestion. Meningeal infiltration may vary from a few lymphocytes to gross exudate. Petechiae and perivascular hemorrhages are described. Perivascular demyelinization with neuroglial reaction may be present. The fundamental lesion is a perivascular demyelinization similar to that seen in other post-infectious encephalidites.

The Scandanavians[9] divide central nervous system involvement in mumps into four clinical types which appears to be an appropriate means of classifying post-infectious encephalidites:

1. *Meningitis:* The symptoms of this group consist of fever, headache, nausea, vomiting, and nuchal rigidity without marked disturbances in the sensorium. They subdivide into para and post-infectious, cases according to whether the symptoms coincide with, or follow, the parotid swelling. In this group they include the latent cases diagnosed only by lumbar puncture, and also the so-called autonomic meningitis which is caused by the mumps virus but where there is no apparent parotid swelling.

TABLE 1

Scandanavian Classification of C.N.S. Involvement in Mumps

1. Meningitis.
   A. Para or Post Infections.
   B. Latent Cases.
   C. Autonomic Meningitis.
2. Meningoencephalitis or Encephalitis
3. Myelitis.
4. Neuritis and Polyneuritis.

2. *Meningoencephalitis or Encephalitis:* In this group the Scandanavians include the rare and dangerous forms of central nervous system involvement which may be noted before, during, after, or without parotid swelling; but which are most frequently seen from the eighth to the tenth day after the onset of parotitis. The symptoms are varied and may include changes in the sensorium, pareses of all types—ocular and facial being the more common. Hemi and monoplegia as well as coma, convulsions, acute ataxia, mental disturbances, and deafness have been noted.

3. *Myelitis:* This is very rare though paraplegia and sphinctural disturbances have been described.

4. *Neuritis and Polyneuritis:* These are also extremely uncommon.

In reviewing the literature in 1918 Casparis[10] noted that nerve deafness was the only residual which was permanent in all cases. It has been estimated that mumps has caused deafness in 5 per cent of the institutionalized deaf in this country.[7] Of twenty-nine cases of mumps meningoencephalitis

seen at the Kingston Avenue Hospital in New York City, over a five-year period, nine patients on follow-up in 1940 revealed evidence suggestive of "minor mental changes."[11] These changes included scholastic retardation, excessive irritability, and nervousness after the illness, fainting spells in emotional situations, and enuresis. Very few attempts have been made to properly evaluate patients whe have had mumps meningoencephalitis.[12, 13]

Mumps meningoencephalitis associated with parotitis and clinically following it usually within three to eleven days is not difficult to diagnose. It affects children and young adults. Males are involved about four times as frequently as females.[7] Cases developing central nervous system symptoms preceding parotid swelling are numerous in the literature.[7, 9, 14–16] The diagnosis of these cases may be made from epidemiological data and the clinical finding of subsequent parotid swelling. The latent case of central nervous system involvement can only be diagnosed by routine lumbar puncture and has been noted many times in the past fifteen years.[9,14,17,18,19] These studies show that the incidence of central nervous system involvement in mumps is higher than would be suspected from clinical findings alone. The diagnosis of mumps meningoencephalitis without parotid swelling may be implied from epidemiological data in some cases[20] but can be made absolutely only by the use of laboratory tests.[21, 22] In a study of 280 cases from the literature, Eberlein and Lynxwiler[7] found 36 cases without apparent parotitis, an incidence of 13 per cent.

As stated by Kilham[21] in 1949, the differential diagnosis of mumps meningoencephalitis without parotitis, non-paralytic poliomyelitis, and lymphocytic choriomeningitis can not be made clinically. Also in 1949, Kilham, Levens, and Enders[22] reported a study of seventeen cases from the Boston Children's Hospital in the summer of 1948 diagnosed tentatively or finally as non-paralytic poliomyelitis. During that summer in Massachusetts there was noted a high incidence of non-paralytic poliomyelitis. At the same time there was an unusual incidence of mumps. From results of serologic tests it was concluded that in six of these seventeen cases the mumps virus was responsible for the disease. In three cases the virus was isolated from the spinal fluid. Full confirmation[21] of the disease is believed to rest on abnormal spinal fluid findings and a fourfold or greater increase in the mumps antibody when serum from the acute phase is compared with a serum specimen taken in convalescence. Successful isolation of the mumps virus gives additional evidence. The skin test should not be used as it may take several weeks to become positive and it may inhibit or stimulate the complement fixing antibody in a person not suffering from the disease.[23]

The treatment of mumps meningoencephalitis is symptomatic. Immune globulin, plasma, and convalescent serum have been suggested but are not

of proven value. The newer antibiotics including aureomycin are being tried in mumps and mumps meningoencephalitis but these have not as yet been sufficiently evaluated.

ANALYSIS OF TWENTY-FIVE CASES OF MUMPS MENINGOENCEPHALITIS FROM CHILDREN'S HOSPITAL

These cases will be presented as a group and only the significant deviations from the usual course of this disease will be discussed. Adequate serological studies were not made on these patients.

In this series of twenty-five cases (Table 2), there were twenty-three males and two females as compared to the 4:1 ratio usually cited. Twenty-one of the patients were white and four were colored. The ages ranged

TABLE 2

Distribution of Cases by Age, Race, and Sex

from three to eleven years. All but four fell into the three year age range from four to seven years.

According to the Scandinavian classification, twenty-two of these cases were mild and they were placed in the meningitis group. In the other three the disease was more severe and they were considered in the meningoencephalitis group. One of these patients was semi-comatose upon admission and had marked nuchal rigidity. This patient did not show clinical evidence of parotid swelling during the course of the disease but there was a history of sibling exposure. Gradual improvement over a four day period was noted and there were no immediate sequellae. Another patient was comatose upon admission and also had a left hemiplegia which had been present for four years following a head injury. This patient also gradually improved over a three day interval and left the hospital without any residuals due to his meningoencephalitis. The third patient in this group was admitted to the hospital because of marked lethargy, aphonia, and slight dysphagia twenty-three days following a mild case of mumps. No peripheral muscle weak-

nesses were noted and the patient was able to obey commands. The dysphagia increased in severity during the first forty-eight hours in the hospital and the child was unable to swallow for one day. During the fourth day, the patient became more alert and was again able to swallow. At the time of discharge on the sixth hospital day speech had not been fully recovered. A recent note from the parents who have moved from this area stated that the boy's speech is normal, but that he had been notably nervous and irritable since his illness in 1948.

There were no cases of myelitis or neuritis in this series.

Table 3 lists the signs and symptoms of these cases in order of their frequency. In the records of these patients, a history of exposure was noted only seven times. Fortunately, a history of intimate exposure was present in the two cases that did not develop parotid swelling. The presenting symptom in one of the cases was severe epigastric pain. Minimal nuchal rigidity was

TABLE 3

Frequency of Symptoms and Signs in 25 Cases of Mumps Meningo-Encephalitis

Fever	25
Parotid Swelling	23
Nuchal Rigidity	22
Nausea and vomiting	21
Headache	20
Change in Sensorium	12
Epigastric Pain	4
Convulsions	2

also noted but there was no headache. The abdominal pain persisted for twenty-four hours. Another patient had crampy abdominal pain accompanied by nausea and vomiting for two weeks following mumps and was dehydrated, lethargic, and cachetic on admission. Generalized convulsions of a few minutes' duration occurred in two cases.

The time of onset of central nervous system symptoms with relation to the parotid swelling is shown in Table 4. In two cases there was never any clinical evidence of parotid swelling. In two cases the neurological manifestations occurred before the parotid swelling. In two cases the central nervous system symptoms and parotid swelling were noted simultaneously. In the remaining nineteen cases, the central nervous system symptoms followed the parotid swelling. The time range for these symptoms being from two days before, to twenty-three days after the parotid swelling with an average of six days for those cases following the parotitis.

Table 5 summarizes the spinal fluid findings. The majority of cases had lumbar punctures performed within forty-eight hours after the onset of neurological symptoms. Repeat spinal taps were done in several cases but

TABLE 4

Relation of C.N.S. Symptoms to Parotid Swelling

C.N.S. Symp. with no swelling	2
C.N.S. Symp. before swelling	2
C.N.S. Symp. and swelling simultaneously	2
C.N.S. Symp. after swelling	19

TABLE 5

Cerebrospinal Fluid Changes

NUMBER OF CASES	DAY OF TAP	CELL COUNT	PER CENT POLYS	PER CENT LYMPHS	PER CENT ENDOTHELIAL	PROTEIN MGM. %
1	2nd	640	30	70		33
2	4th	38	0	100		7
3	2nd	178	22	78		25
4	3rd	1050	40	60		87
5	3rd	33	4	96		12
6	1st	400	26	71	3	40
7	2nd	290	30	64	6	40
8	2nd	155	56*	44		19
9	2nd	585	10	90		35
10	2nd	291	31	69		25
11	2nd	203	4	86	10	15
12	2nd	380	30	69	1	70
13	2nd	450	28	69	3	25
14	14th	190	15	80	5	20
15	2nd	76	52*	46	2	200
16	2nd	780	18	82		40
17	1st	16	50*	50		15
18	1st	1125	38	62		72
19	1st	160	14	85	1	30
20	1st	160	11	87	2	10
21	7th	212	24	76		154
22	1st	255	56*	44		21
23	4th	650	65*	33	2	35
24	3rd	434	42	58		10
25	2nd	872	32	67	1	40
Averages	2.7	384	30	70		43

* Polymorphonuclears equal to or predominating over lymphocytes in these cases.

only the initial findings are recorded in this table. The white cell counts ranged from 16 to 1125 per cubic millimeter with an average of 384 cells per cubic millimeter. Lymphocytes predominated in the average differential count but not so markedly as noted in most series. In five of these cases polymorphonuclear cells equaled or slightly outnumbered the lymphocytes. The protein was elevated above 25 milligrams per 100 cubic centimeters in thirteen instances. The sugar was normal in all the spinal fluids.

SUMMARY

1. The literature on the subject of mumps meningoencephalitis is surveyed and an analysis of twenty-five cases from the Children's Hospital is presented.

2. A practical clinical classification of the central nervous system involvement in mumps is reviewed.

3. The value of laboratory procedures in the differential diagnosis of the encephalidites and non-paralytic poliomyelitis is emphasized.

4. A more thorough follow-up program is indicated to ascertain the incidence of less apparent residuals such as personality changes and intelligence impairment.

5. The need for awareness of mumps meningoencephalitis occurring without parotid swelling or with delayed swelling is illustrated by four cases in this series.

DISCUSSION

Lawrence Kilham, M.D.

This has been an interesting summary of experience with mumps. I should like to comment on the serological diagnosis of this disease, which may be of special importance in cases of meningoencephalitis without parotitis in which a diagnosis is often difficult to establish clinically. Serum specimens should be obtained as soon after onset of illness as possible and again a few weeks later in convalescence. Such paired sera will usually reveal a diagnostic rise of antibody titer. It is sometimes difficult to establish a diagnosis on a single serum specimen. As antibodies frequently appear at or soon after the onset of mumps, it is important to obtain the first serum specimen early in the course of illness. The complement fixation test has been widely used for the serologic diagnosis of mumps. In our experience and in that of others, the antihemagglutination test is just as reliable as the complement fixation test and has the advantage of being far easier for an average hospital laboratory to perform. Mumps virus can be isolated from the cerebro-spinal fluid fairly readily in cases of mumps meningoencephalitis. This procedure, however, is more of a research tool than a diagnostic method.

In regard to the skin test, a number of investigations have shown it to be a fairly reliable index of past infection with mumps virus when positive. Although it may become positive soon after onset of illness, skin testing would appear inadviseable as a clinical procedure at the present time. Once an individual has been skin-tested, future serologic studies cannot be carried out reliably. The reading of a skin test might be quite difficult for anyone not experienced in its use. Skin testing material is now available commercially. Its principal use would seem to be as a test of susceptibility in individuals who might benefit by vaccination.

Mumps vaccine has also become available commercially, although its effectiveness and limitations have not been fully demonstrated. It is not known how many injections an individual should receive, what percentage of those vaccinated will be fully protected, and how long protection will persist. For these reasons it may be inadvisable to vaccinate children. Such a procedure might only postpone an attack of mumps until later years when it would be more severe as well as inconvenient. Mumps vaccine may be of greatest value for certain individuals, such as a father exposed to his children, where circumstance might make an attack of mumps undesirable.

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ERYTHEMA BULLOSUM MALIGNANS-PLURIORIFICIAL TYPE (STEVENS-JOHNSON DISEASE)

Report of a Case Treated with Cortisone

Case Report No. 196

Harold T. Yates, M.D.
Crenshaw D. Briggs, M.D.
William A. Anderson, M.D.
Fernando R. Leyva, M.D.
Ellery Michaud, M.D.

Although the number of cases reported in the medical literature has increased rather rapidly in recent years, Erythema Exudativum Multiforme is still to be considered one of the rare diseases encountered in practice. As one peruses the literature, one is impressed with the gradually increasing severity of the cases reported.

Few diseases have been designated by more terms than this one in the eighty odd years since Bazin first reported the mild form in 1862. The most constant finding, though varying greatly in degrees of involvement, has been the rash.[19] It has been reported as ranging anywhere from the usual maculopapular rash of a pink, red, or violescent hue symmetrically distributed over the neck, face, back, chest, and extensor surfaces of the extremities,[3] to the vesicular, bleb, or bullous type affecting the same

areas. The next most constant and more important finding has been the ocular involvement.[6, 7] This, likewise, has varied in severity from simple conjunctivitis to iritis, keratitis and corneal ulceration. In 1866 von Hebra[15] reported the involvement of the mucous membranes of the mouth and eyes. More importance was attached to this involvement of the mucosa of the eyes and mouth by Kaposi[14] in 1893. It was Rendu[20] in 1916, who first emphasized the severe constitutional symptoms and fever which accompany the disease. He and Fiessinger[21] considered this a new syndrome and attached to it the name ectodermosis erosiva pluriorificialis.

Stevens and Johnson[2] in 1922, reported their now classic series of two cases of eruptive fever associated with stomatitis and ophthalmia. They too felt that this was a disease entity, and since that time the disease has become known as the Stevens-Johnson Syndrome or Disease.

Both Costello[13] and Soll[12] reported large series of cases of the disease in 1947. Some of those cases recorded by Costello were so toxic that he felt they were better classified as erythema bullosum malignans-pluriorificial type. One wonders then if this disease is not becoming more virulent with passing time, and whether these cases should not all be considered under one classification and subgrouped according to the degree of toxicity.

We feel that our case fits into Costello's newer classification of the disease because of the severe degree of toxicity it presented. This case is important for several reasons: first, it presented a great problem in fluid and electrolyte balance; second, it, we believe, was the first case ever treated with Cortisone; third, to our knowledge, it was the first case complicated by a *Pseudomonas aeruginosa* septicemia.

There is a tendency in the literature to overlook the few cases which have had a fatal outcome and to stress the self-limited nature of the disease. It is our feeling that whether these cases are becoming more severe on the whole or whether some are just a great deal more toxic than others, the actual severity of the syndrome should be emphasized in the literature. There seems to be no better way to accomplish this than to report a very severe case and to present the marked changes in the blood chemistry encountered during the extremely toxic condition.

This disease is usually encountered in the spring and fall. It is not limited geographically. Any age group in either the white or colored race can be affected. It occurs about five times more frequently in the male sex. Recurrences have been reported by Ritter,[17] Rosenberg,[16] and Keil[1] in their cases.

The pathology is limited to the superficial layers of the skin and mucous membranes. There is inflammation of the affected areas with edema, perivascular round cell infiltration and varying degrees of separation of the epithelium from the corium in the skin depending on the degree of in-

volvement.[4] These changes may be associated with cracking of the mucous membranes in the mouth, greyish pseudomembraneous exudates and sloughing of the entire buccal, pharyngeal, and gingival mucosa. The conjunctivae are usually affected to a certain degree by the same pathological processes. A purulent discharge from both eyes is the rule.[16, 9] Ruptured blebs leading to corneal ulcerations are frequently encountered. The mucosa of the intestinal tract has been involved giving rise to bleeding and black stools. The mucous membranes of the urethra and vagina are affected by bleb or bullous formation followed by complete denudation of the affected areas.

No specific etiology is known. It has been suggested that this is a virus disease associated with the virus of Herpes Simplex. These individuals are thought to harbor the virus, and when their resistance is lowered for any reason, they react with the rash of Herpes Simplex. Some feel that this is an infectious disease mainly because of the fever and septic course followed by many of the patients. In the seasonal cases of erythema multiforme one finds some foci of infection in the tonsils or accesory sinuses. These foci are thought to do one of two things: first, they may shower the blood stream with micro-organisms which are disseminated to the various organs of the body involved; second, these foci can produce allergizing substances which are transmitted by the blood stream to the different organs of the body sensitizing those particular tissues. This disease has been reported after the administration of sulfa drugs, anticonvulsants, sedatives, virus or bacterial infections,[8] vaccines, serums, or exposures to sunlight.

Complications of this disease are relatively few considering the extreme toxicity which can prevail. Among these are nephritis, nephrosis, bronchopneumonia, vaginal strictures, uremia, furunculosis, and carbuncles. The ocular complications are the most important. A high percentage of these cases result in defective vision ranging from dimness of vision to total blindness. One case of intussception following intestinal lesions has been reported. Our case adds a new complication of a serious nature in *Pseudomonas aeruginosa* septicemia. Although the usual habitat of this organism is the ground, it is also found on the skin. Therefore, it can present a problem when one considers the extensive skin involvement in some of these patients.

Treatment is palliative and supportive. The importance of blood, plasma, and albumin as well as chlorides and other electrolytes can best be understood from the case presented. Aseptic care of the skin as far as possible following the accepted treatment of second degree burns is mandatory in the more severe cases. Antibiotics[5] and chemotherapy are essential to prevent secondary infections and to prevent, if possible, irreparable damage to the eyes. Large doses of multiple vitamins and vitamin K are part of the usual treatment.

CASE REPORT

M. P., a six and one-half year old white male, was admitted to Children's Hospital, Washington, D. C. on June 26, 1950 complaining of sunburn, sore mouth, fever, mild itching, and slight pain in the skin of two days' duration. Four days and again three days prior to admission the child was exposed to the sun for periods of six and eight hours respectively while playing in white sand. Two days prior to admission the lad complained to his mother that he had sand in his eyes and mouth causing a gritty sensation. At that time his temperature was 103.0 F. He complained of headache, generalized aches and pains, and slight photophobia.

Physical examination at home the day of onset of his symptoms revealed bilateral bulbar and palpebral conjunctival injection and inflammation without discharge; one small ulcerated area on the left anterior pillar of the pharynx; a similar lesion on the soft palate above the uvula; generalized increased erythema and injection of the mucous membranes of the pharynx, palate, and mouth; slight erythema of the shoulders; more marked erythema of the entire back extending up onto the neck; and generalized increased skin temperature with good turgor, in addition to the photophobia.

It was felt that the child had a mild sunburn, ultra violet conjunctivitis, and herpetic pharyngitis. Treatment consisted of fluids, aspirin, sponges, and enemas as needed. The child's temperature went up to 106.0 F. the evening after examination.

By the second day he had developed a slight maculopapular rash over the shoulders and temporal areas. The rash over the back and neck had become more violescent. There was a faint macular rash appearing over the anterior surfaces of both thighs. The ocular symptoms were decreasing and the conjunctivae were clearing. The ulcerations in the mouth were spreading. Although fluids were being taken freely by mouth there was marked dysphagia. The temperature spiked to 105.0 F. during the second day. Penicillin intramuscularly as Duracillin fortified was given both during the morning and evening in 600,000-unit doses.

The morning of the day of admission the temperature was down to 101.0 F. The rash was spreading over the chest in a macular pattern. The previously involved areas of the shoulders, back, and neck were becoming more confluent and violescent with vesicular and bleb formation. The mouth lesions were spreading rapidly. The eyes were becoming more inflamed and the photophobia more marked. There was an intermingling of itching and pain associated with the rash. The dysphagia became very marked, and during the day the fluid intake dropped to practically nothing. Parenteral penicillin was continued twice daily. During the afternoon before admission the blebs over the back became bullae.

At the time of admission the child was moderately toxic. His temperature was 104.8 F. Physical examination revealed markedly ulcerated, cracked, boggy, foul, bleeding mucous membranes of the mouth and pharynx. There were bullae over the back and neck. There was a violescent rash over part of the back, face, chest, and anterior thighs. A faint punctate rash was beginning over both feet. The involvement of the skin had been and continued to be symmetrical.

Shortly after admission the child was seen by one of us who began treatment of the extensively involved areas of the skin with sterile rayon strips and pressure dressings. The entire back, neck, chest, and shoulders were included in the dressings. Other treatment consisted of Duracillin fortified 400,000 units twice daily, intravenous fluids, Chloromycetin 250 milligrams every six hours, mouth washes, and sedatives every four hours. Figure 2 shows the problem presented by the disturbance in blood chemistry. It was necessary to give this child codeine every three to four hours for several days to relieve his pain.

On the second hospital day the child was more toxic. Fetor oris increased. There was bleeding from the mucous membranes on any attempt by the child or examiner to open his mouth. The conjunctivae were becoming wildly inflamed, and a purulent ocular discharge became profuse. There was periorbital edema, as well as moderate edema of the face, hands, and arms.

It became apparent by the third hospital day that we were dealing with a case of Erythema multiforme bullosum of the Stevens-Johnson type. With each hospital day the child became increasingly more toxic. There was considerable concern over his prognosis in spite of the reputed self limited nature of the disease. The lad was in negative nitrogen balance. His chlorides were remaining low in spite of large amounts of intravenous fluid. The rash was spreading over the lower part of the abdomen, arms, and legs with varying-sized bullae. There was a positive Nikolsky's sign. Tremendous amounts of serum were being lost as these bullae broke.

By the fifth hospital day the child had become so edematous generally, and his rash had spread to involve so much of the skin that it was necessary to do a venesection. Continuous fluids as determined by the blood chemistry reports were administered. By this time the child could open his eyes only with excruciating pain. In spite of eye washes the purulent discharge was profuse enough to cause the lids to be stuck together. Bullae over both eyes became hemorrhagic. A typical herpetic lesion developed over the upper lip. It spread to involve both nares and the lower lip. By the eighth day he had a typical eschar involving the lips and extending into the nares.

On the sixth hospital day the child's condition was so critical that it

was deemed advisable to resort to any therapy which might improve his obviously poor prognosis. Since we were dealing with a disease which was thought to be largely allergic in nature, we placed the child on Cortisone therapy. The Cortisone regime consisted of 50 milligrams every eight hours for six doses; then 50 milligrams daily for two doses; then 25 milligrams daily for two doses; then 12½ milligrams daily for two doses; then 6 milligrams daily for two doses. During Cortisone therapy potassium chloride was administered by mouth. An attempt was made to restrict fluid intake and at the same time to keep the child in proper nitrogen and electrolyte balance.

Within thirty-six hours after Cortisone therapy was started on this child, he showed a dramatic improvement. The extreme toxicity was rapidly lessening. There was a dramatic improvement in the foul condition of the child's mouth. He started taking fluids in the form of weak tea and protein milk with no trouble within forty-eight hours after Cortisone was started. The rash was spreading over the lower part of the body and extremities. There was involvement of the scrotum and penis. The mucosa of the glans became edematous; then a large bleb formed over the entire glans into which the child was urinating. The urine was seen to squirt out from the detached edges of the bleb at the glans corona.

On the ninth day when the dressings were changed the child first complained of some pain in his right back. On the tenth day after receiving 100 milliliters of salt-free albumin, there was a sudden spike in temperature to 106.8 F. This responded rapidly to aspirin, packs, and enemas. For three days there was an unexplained morning and afternoon spike in his temperature as seen in Figure 1. The venesection needle was removed on the thirteenth day. There was a minimal amount of discharge from that site. During the eight days the venesection was kept in constant use a total of 1750 milliliters of plasma, 700 milliliters of human salt-free albumin, 500 milliliters of whole blood and 5750 milliliters of 5 per cent glucose in distilled water was administered.

The child's temperature became normal on the fourteenth hospital day. The dressings were removed from the back, chest, and neck on the seventeenth day. Except for inconstant and varying degrees of right flank and right lumbar pain which at times was exquisite, the hospital course was uncomplicated.

On the twenty-third day, with no symptoms except the myalgic pains in the right lumbar and iliosacral areas, the lad's temperature went to 101.0 F. Chloromycetin was discontinued on the twenty-fourth day at which time the temperature was normal. The back pains continued. The temperature rose to 102.0 F. on the twenty-fifth day, and it continued to spike daily as is shown in Figure 1. Agglutinations, urines, urine cultures, and blood cultures were negative. Urological consultation was requested

to rule out perinephretic abscess or psoas abscess. An intravenous urogram done on the twenty-seventh day was negative.

The child was started on Terramycin 500 milligrams every six hours after blood cultures were drawn on the twenty-ninth day. At that time he was complaining bitterly of the pain in his back and side. The point of maximum intensity of the pain had shifted to the left side. On the thirty-second day the last blood culture was reported as positive for *Pseudomonas aeruginosa*. Terramycin was increased to 500 milligrams every four hours, and ½ gram of Dihydrostreptomycin sulfate twice daily was started. Sensitivity

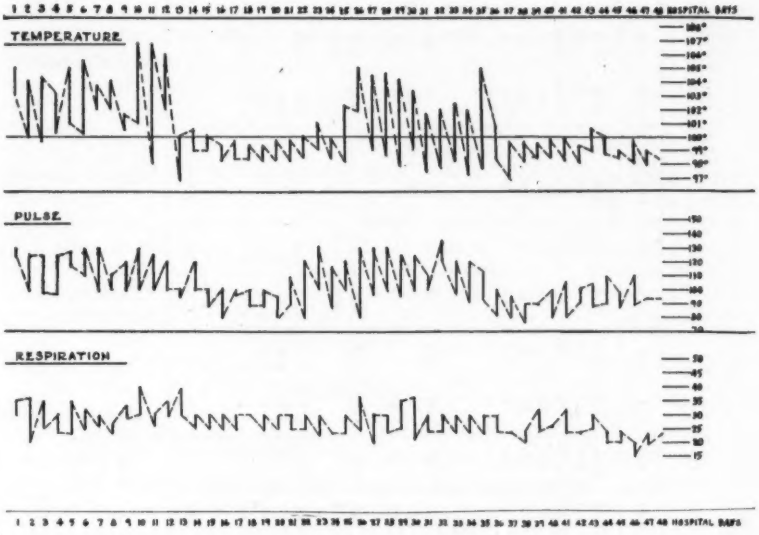

FIG. 1

tests were set up against Terramycin, Aureomycin, Chloromycetin and Streptomycin with the results shown in Figure 4. Terramycin was discontinued and Chloromycetin was started both by mouth in doses of 500 milligrams every four hours and intravenously in doses of 250 milligrams twice daily. The third intravenous dose of Chloromycetin precipitated a violent reaction evidenced by marked cyanosis of the head, neck, and shoulders; rapid thready pulse; and extreme anxiety. The blood pressure was not recorded. In addition to the Chloromycetin and Streptomycin the child was treated with blood transfusions every other day.

On the thirty-third day a small "reddened area the size of a pea" ap-

DATE	6-24	6-27	6-29	6-30	7-2	7-3	7-4	7-5	7-8	7-12	7-13	7-15	7-21	7-22	7-25	7-26	7-28	7-31	8-1	8-3	8-7	8-9
Hgb. gm/100 cc.	10.5	11.0	14.8	15.0	11.5	13.0	13.0	14.0	12.2	12.0		12.0	13.9			13.9	15.0			14.0		
Erythrocytes	3.75	3.6	4.0	5.5	3.5	3.5	4.2	3.6	3.0	4.6		4.6	4.3			4.1	4.6			4.4		
Leucocytes	5,500	2,900	5,700	8,300	11,300	7,500	7,000	7,600	7,200	8,600		18,300	10,000			9,000	9,400					
Neutrophiles	63	62	76	73	78	76	77	78	65	75		90	76			76	85					
Segmented	57	59	73	72	68	72	63	68	64	70		79	73			72	72					
Staff	6	3	3	1	10	4	14	10	1	5		9	3			3	9					
Metamyelo												2				1	4					
Eosinophiles				2						1		1				3	6					
Basophiles										1												
Lymphocytes	37	38	24	25	22	22	23	22	35	23		9	26			21	9					
Eosinophile Count				102		24	0	0		63	159	100		114					207			
E. S. R.				22	33	42						40	50			48		28		16	24	14
Hematocrit	37																					
Chlorides		430	429	396	527	439	439	468	477			450	326		317							
Potassium				16.8				16.0	14.2				19.2		32.1							
Sugar				110																		
Total Protein		4.61	4.07	4.68	6.04	6.12	6.15	5.31	5.01			5.95	6.09									
Albumin				3.22	3.75	4.21	4.9	4.12	3.7			4.32										
Globulin				1.46	2.29	1.9	1.25	1.19	1.31			1.63										
A/G Ratio				2.2/1	1.6/1			3.4/1	2.8/1			2.7/1										
NPN mg.%		24.3							34.4													
CO_2		52.0																				
Sodium				305				273	304													

FIG. 2

peared in the venesection site. This was incised and the culture grew out *Pseudomonas Aeruginosa*. A blood culture taken on the thirty-fourth day was reported negative. The temperature chart shows that the course was back to normal by the thirty-sixth day.

URINE

AMT. IN CC./24 HRS.	6-25	6-27	7-1	7-3	7-5	7-11	7-12	7-13
			1500	900	910	1100	1850	2200
Appearance	Cloudy	Cloudy		Turbid				
Reaction	Acid	Acid		Acid				
Specific Gravity	1022	1021		1020				
Albumin (mg/100 cc)	10			80				
Sugar								
Acetone	1+	1+						
Microscopic	4-5wbc			Rare wbc & rbc				
Chlorides (mg%)			83.0	17.0	17.0	380.0	330.0	272.0
Creatinine			32.3	33.3	30.3	28.6	18.8	16.7
Uric Acid			32.5	34.0	37.8	42.5	22.5	18.5
Total Chloride gms.			1.2	0.15	0.2	4.2	6.1	6.0
Total Creatinine			0.48	0.30	0.28	0.31	0.35	0.37
Total Uric Acid			0.49	0.31	0.34	0.47	0.41	0.41

FIG. 3

BACTERIOLOGY

Throat Culture:

6-25: Shows normal flora.

Blood Cultures:

6-27: Negative for growth in 24 hours, 6 days, and 14 days.

7-19: Negative for growth in 24 hours.

7-20: Positive for contaminates in 24 hours.

7-22: Positive for *Pseudomonas Aeruginosa*.

7-26: Negative in 24 hours.

7-27: Negative in 24 hours.

Urine Culture:

Positive for *Micrococcus pyogenis* var. *aureus*, rare micro. and fecalis.

Sensitivity tests on Pseudomonas aureus:

Resistant to Terramycin, 20 mcg. of Aureomycin, and 10 mcg. of Chloromycetin; and sensitive to 0.1 mcg. of Streptomycin.

Culture from venisection site:

Positive for *Pseudomonas aureus;* sensitive to 0.1 mg. Streptomycin.

FIG. 4

All antibiotic therapy was discontinued on the forty-second day. At that time the lad was up and about the floor. He continued to improve and was discharged on the forty-eighth day when examination revealed a mild

FIG. 5. Fifth hospital day showing eschar about the mouth and hemorrhagic bullae above the eyes and marked periorbital edema.

FIG. 6. Seventh hospital day showing the symmetrical bullae of the forearms, lower abdomen, scrotum, and glans penis. Also note serous-soaked dressings.

FIG. 7. Showing hemorrhagic bullae of the face and neck and a large bullus of the lower abdomen and marked Hyperemia of involved area in contrast to normal skin of the surgeon's arm.

palpebral conjunctivitis with no decrease in visual acuity and widespread areas of hyper and hypopigmentation of the skin.

FIG. 8. Ninth hospital day after pressure dressings had been removed showing wide areas of denudation and bleeding.

FIG. 9. Tenth hospital day showing the hemorrhagic involvement of the bullae of the abdomen, scrotum and symmetrical blebs and bullae of the lower extremities.

COMMENT

From this case presentation it is quite obvious that Erythema Bullosum Malignans is in certain instances an extremely toxic disease requiring constant medical care. The self-limited nature of the disease can be assumed only if constant supervision is carried out most meticulously. On several

occasions this lad was so toxic and critically ill that he was carried on the danger list. The extreme importance of supportive therapy in the form of parenteral fluids to maintain positive nitrogen balance and electrolyte balance cannot be overemphasized.

This case began after a generous exposure to the sun rays. It would seem justifiable to attribute this case to an allergic reaction. Whatever the precipitating factor may be in these cases, it seems most likely that the trigger mechanism which fires the malignant type of skin and mucous membrane reaction with severe toxic constitutional symptoms is definitely an allergic one. We realize that only Patz[11] and Herronen[18] have reported any increase in the eosinophile counts of their cases. However, the drugs now reported to be effective against virus infections were ineffective in this case during the active stage of the Erythema Bullosa Malignans. On the other hand, the dramatic response to Cortisone lends support to a possible allergy as the etiology in this disease. Certainly this suggests Cortisone as a drug worthy of trial in future cases. The use of ACTH or Cortisone in the treatment of other cases of this disease may well help to settle the question of its etiology.

The virulent nature of this case warrants its classification under that suggested by Costello as the Erythema Bullosum Malignans-Pluriorificial type.

The finding of *Pseudomonas aeruginosa* septicemia presents an additional complication in this disease. The importance of sensitivity tests to antibiotics and the scientific manner in which they can correctly direct therapy are borne out by the results obtained here. Attention should be called to the sedimentation rates. Although this boy showed rapid clinical improvement on Cortisone, the sedimentation rate continued to rise. The delayed positive blood culture bore out the fact that the sedimentation rate was pointing to active infection which at the time was not manifested by any positive physical findings.

The successful outcome of this case is a glowing tribute to the great degree of coordination and team work consisting of astute residents, conscientious nurses, efficient and persevering laboratory technicians, and the painstaking specialists who were called in at all hours on short notice to assist the pediatricians in evaluating different findings.

SUMMARY

A short history of the disease known as Erythema Exudativum Multiforme has been presented.

The incidence, pathology, etiology, complications, and treatment of this disease have been reviewed.

A severe case which fits Costello's classification of Erythema Bullosum Malignans-Pluriorificial type has been reported.

An attempt has been made to emphasize the importance of nitrogen and electrolyte balance in handling these severe cases.

The first use of Cortisone in the treatment of Erythema Exudativum Multiforme is believed to be reported here.

A possible allergy as the etiology of this disease is stressed in connection with the case reported.

The great value of sensitivity tests in the treatment of severe infections with our present day antibiotics is exemplified.

The first case of Erythema Exudativum Multiforme complicated by *Pseudomonas aeruginosa*, and the successful treatment of that complication with Chloromycetin and Streptomycin is reported.

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SACROCOCCYGEAL TERATOMA

Case Report No. 197

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Definition. A teratoma is *a true tumor* or neoplasm composed of *multiple tissues* of *kinds foreign to the part* in which it arises. It is a true tumor in the fact that it displays some degree of progressive uncoordinated growth and is not merely a quiescent malformation. Teratomas contain multiple tissues even in the simplest "dermoid cysts," because in addition to skin and its appendages, proper study will reveal other kinds of tissue, such as neural, skeletal, dental, respiratory, and alimentary. These tumors contain tissues foreign to the part in which they are found; and are composed of tissues from all parts of the body. (Willis[1])

Etiology. It is possible in the formation of germ layers that the cleavage may be incomplete and portions of one layer may be carried over into another. On the other hand, it is important to consider the budding of originally simple embryonal tissues giving rise to embryonal inclusions. (Ewing[2]). The embryonal structures which give rise to the sacrococcygeal growths are chiefly:

1. The fovea coccygea and the coccygeal vestiges of the neural canal.
2. The neurenteric canal.
3. The post anal gut.
4. The proctodeal membrane.

Classification. Perhaps the classification of teratomas into those composed wholly of mature tissues and those containing embryonic tissues is the most practical because this is of more value for prognosis. Attempts to classify these tumors as cystic or solid is poor since teratomas have both elements in variable degrees. The classification of teratomas into monodermal, bidermal, and tridermal is also inadequate because a thorough study will always reveal the three-dermal element. (Willis[1]).

Sites of Occurrence. Willis[1] in a review of 82 cases reports that teratoma occurred in the following locations:

1. Ovary—50 cases (42 benign and 8 malignant).
2. Testis—19 cases (All malignant).
3. Epididymis—2 cases (Both benign).
4. Retroperitoneal—3 cases (All benign).
5. Presacral—2 cases (Both benign).
6. Anterior mediastinal—3 cases (All benign).
7. Intrapericardial—1 case (Benign).
8. Brain—2 cases (Both malignant).

Incidence. In a review of the literature Chaffin[3] summarized the clinical aspects of sacrococcygeal teratomas of 72 cases. In 59 cases the sex was specified: 13 were males and 46 were females. Fourteen of the patients were stillborn; 11 died in a few days. Forty-five of the 72 cases received operative treatment. Calbet[4] reports that congenital tumors of the sacroccygeal region occur once in every 34,582 births. Teratomas make up a small percentage of these tumors. Riker and Potts[5] reviewed 600 tumors at Children's Memorial Hospital in Chicago and found 7 sacrococcygeal teratomas or a 1 per cent incidence.

Clinical Aspects. Sacrococcygeal teratomas have their origin retrorectally and attach to the coccyx or sacrum. They usually grow downward and posteriorly into the buttocks displacing the anus forward and to one side. They may extend upward behind the rectum and present as an abdominal mass. They vary in size from a small lump to a huge mass and are covered with skin which may have ulcerations or fistulae. Physical evaluation other than examination of the local presenting mass must include abdominal, pelvic, and rectal examinations. X-ray study should be made not only to demonstrate dentitions, ossification, and calcifications, but also to reveal any bony defects of the vertebrae or pelvis.

Differential Diagnosis.

1. *Meningocoele.* Meningocoeles are smaller than teratomas and do not increase in proportion to the infant growth. A meningocoele is covered by a translucent membrane whereas a teratoma is covered with skin. Rectum is not often displaced by a meningocoele. Usually there is evidence of a communication between a meningocoele and the spinal canal. This is evidenced

by expansion of the tumor with coughing and crying, or bulging of the fontanelle upon compression of the mass. Neurologic signs in the lower extremities are more often associated with meningocoele. X-ray evidence of spina bifida suggests meningocoele. (DeVeer and Browder[6]).

2. *Chordoma.* Chordomas are remnants of the primitive notochord which are characterized by a progressive slow growth with a tendency to invade and destroy bone by direct extension. Pain is often present. They occur between the ages of 40 and 70 with 68 per cent in males; whereas, teratomas are usually found at birth (90 per cent recognized at birth—Riker and Potts[5]) and occur predominately in the female. Chordomas tend to recur after removal and are only slightly radiosensitive.[12]

3. *Ependymoma.* Ependymomas are extremely slow-growing neoplasms which produce the same symptoms as chordomas. They occur only half as frequently as chordomas and are found in a younger age group. Neurologic symptoms are more frequent. Destruction of bone by an ependymoma is the result of erosion from pressure. Chordomas yield very poor surgical results whereas ependymomas are frequently amenable to surgery.[7]

4. *Giant cell tumor of the sacrum.*
5. *Neurofibromas.*
6. *Neuroblastomas.*
7. *Ganglioneuromas.*
8. *Lipoma.*
9. *Fibroma.*
10. *Fibrosarcoma.*
11. *Sarcoma.*
12. *Hemangioma.*
13. *Lymphoblastoma.*
14. *Myeloma.*
15. *Tuberculosis of the Sacrum.*
16. *Rectal Carcinoma.*

Complications of the Tumor.

1. *Malignancy.* The malignant tumors developing in sacrococcygeal teratomata have occasionally been observed but are considered to be extremely rare. Riker and Potts[5] reported an incidence of 15 per cent malignancy. In 1942 Lisco[8] reported a total of 12 cases, 10 of which were accrued from the literature. There was an equal distribution between males and females. Fifty per cent of the malignancies were papillary adenocarcinoma; 25 per cent, adenocarcinoma; 16 per cent, sarcoma; and 8 per cent, embryonal carcinoma. Willis[1] states that the malignancy of a formerly benign cystic teratoma is most often a squamous cell carcinoma from the skin and that papillary adenocarcinoma has been seen. Another type of malignant teratoma is one in which all of the component tissues are actively multiplying

and there is metastasis of the composite structure. The third type is a relatively benign teratoma which metastasizes by peritoneal dissemination.

2. *Ulceration, Fistula,* and *Infection.* Teratomas of the sacrococcygeal variety are prone to develop ulceration with superimposed fistula and infection. The ulcerations of the skin are due to pressure necrosis of the mass and to impaired blood supply. The location near the anus predisposes it to secondary infection.

3. *Obstruction of the Rectum or Urinary Tract.* This phenomenon is usually dependent on the size of the presacral portion of the nass. All of the sacrococcygeal teratomas are closely adherent to the posterior portion of the rectum and are considered to have their origin retrorectally. If the mass grows mostly in the presacral area, then the sacrococcygeal teratoma will present as an abdominal mass and by its size compress the rectum or the bladder and produce obstruction of either organ. (Woodruff[9]).

4. *Hypersecretion of Some Endocrine of the Tumor.* Endocrine effects may be produced depending largely on the structural composition of the tumor.

5. *Position* and *Size* of the *Tumor* may incapacitate the patient. Large teratomas may cause dystocia (Neal[10])

Treatment. Riker and Potts[5] advise that a posterior approach be used in all cases of sacrococcygeal teratoma for several reasons:

1. Complete removal is easiest with this approach; in addition, the coccyx can be resected if necessary.

2. The peritoneal cavity is avoided.

3. Hemorrhage is more easily controlled because the blood supply is located mainly in the posterior region.

4. Local recurrences in the scar are easily seen and treated. McKnight[11] states that with removal of sacrococcygeal teratomas, the patient frequently exhibits shock which is out of proportion to the amount of blood loss. Routine transfusions are indicated during the operative procedure.

Results of Treatment. Chaffin[3] found in his series of 72 patients that 45 were surgically treated. Twenty-five patients were stillborn or died in a few days. Of the 45 treated patients, 28 were under the age of one year; 18 or 64 per cent recovered. There were 4 patients between the ages of one to two years and 6 between four and eighteen years of age. Seven (70 per cent) recovered. The remaining patients were between the ages of twenty to sixty years of which 2 or 33 per cent were cured.

CASE REPORT

B. B., a white male newborn infant, was admitted to the Children's Hospital at the age of two days with the chief complaint of a mass over the buttocks which was present at birth. The pregnancy, labor and delivery were normal. Delivery occurred at term.

The family history was non-contributory.

Admission physical examination revealed a well developed, well nourished white male infant. The positive physical examination was limited to the sacrum and buttocks. Over the buttocks and sacrum a large mass was present measuring 8 x 3 x 3 centimeters, the greater part was in the left buttocks. Just to the left of the midline was an area of ulceration $1\frac{1}{2}$ x 3 centimeters in length which was packed open with vaseline gauze. It was in this area that the tumor was extremely firm. Palpation of the remainder of the tumor revealed it to be soft and cystic. There was some growth of hair present on the skin overlying the tumor. Rectal examination was negative in that no masses could be palpated. The extremities were normal with normal motion of the lower extremities.

Admission laboratory data revealed a hemoglobin of 14.2 grams; 5,300,000 red blood cells; 28,000 white blood cells with 55 polymorphonuclears, 39 lymphocytes, 2 eosinophiles, and 4 monocytes per 100 cells. The urinalysis was negative. X-ray examination of the lower thorax and lumbar spine and the pelvis in the A-P and lateral views revealed a soft tumor mass in the region of the buttocks. Several calcific shadows were observed within the tumor mass.

On the second hospital day the child was taken to the operating room and by the use of the posterior approach the entire teratomatous mass was dissected free and removed completely. It was adherent to the sacrum and coccyx but it was not necessary to sacrifice any of these parts. It was attached to the posterior aspect of the rectum but at no point did it seem to have invasive qualities. A small tissue drain was placed down into the presacral area and brought out through the midline of the incision. On the second post-operative day the drain was removed. On the fourth post-operative day the sutures were removed and it was necessary to irrigate the wound with normal saline four times daily. The patient was on antibiotics at all times post-operatively and received a transfusion during the operation. The posterior wound gradually filled in at its midportion so that only a small dimple remained. The remainder of the hospital stay was uneventful. He was discharged on the twenty-eighth hospital day with a normal weight gain and tolerating an evaporated milk formula well.

SUMMARY

1. A case of sacrococcygeal teratoma with a successful surgical removal is reported.

2. The differential diagnosis and complications of this type of tumor are discussed.

3. The tumor is best treated by surgical removal through a posterior approach.

4. The results of treatment indicate that with early removal the mortality rate is lower.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.

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By Invitation: John A. Washington, M.D.

Sanford Leikin, M.D.

This six month old white male was first admitted to this hospital on September 19, 1950 where he remained for three days and was then discharged. He was readmitted on September 29, 1950 and died during this admission on October 2, 1950. The history revealed that the patient was born at a local hospital and had persistent cyanosis from birth. He became more cyanotic when excited. The patient was hospitalized for one month and the diagnosis of congenital heart disease was made. About one week prior to the first admission the mother noted left-sided contractions of both extremities beginning with tremors and then gross, jerky movements.

Physical examination during the first admission revealed a well developed, obese, white male who was cyanotic even at rest. Examination of the head, neck, ears, nose, and throat gave negative findings. The chest was clear to percussion and auscultation. The respiratory rate was rapid. The heart was not enlarged to percussion. Several observers heard no murmur. The liver was palpable two finger-breadths below the right costal margin. On hospitalization, the episodes, which the mother described as convulsive movements, occurred only when the child became exceedingly dyspneic and cyanotic. As soon as the cyanosis and dyspnea were relieved with oxygen, the tremors of the left side of the body ceased. The patient was discharged on September 22, 1950 as improved.

On the second admission on September 29, 1950 the history disclosed that the patient developed an upper respiratory infection with some fever, cough, and nasal discharge. He was treated by his local physician with aureomycin with good results. The night before admission the infant was accidentally burned with a water bottle and a second degree burn of the right thigh resulted. The local physician advised admission. Physical examination on this last admission disclosed:

General—A cyanotic white male infant in no acute distress.
Head—Normal size and shape, no masses or tenderness.
Ears, nose and throat—Negative
Neck—Supple
Chest—Expansion equal and bilateral.
Lungs—Clear to percussion and ausculation.
Heart—Rate rapid and rhythm regular. No murmurs.
Abdomen—Soft, no masses felt; liver not palpable.
Extremities—Large blister inner thigh on the right.
Neurological—Negative.

There were no laboratory examinations on the last admission. The following are from the previous hospitalization at another institution: red blood cells, 6,400,000; hemoglobin, 16 grams; white blood cells, 8500 with 33 neutrophiles, 1 eosinophile, 1 basophile, and 65 lymphocytes per 100 cells. Urinalysis was negative. Electrocardiogram on September 19 showed left ventricular hypertrophy. Fluoroscopy performed two days and again at five months showed slightly widened cardiac shadow which in the oblique seemed to be due to enlargement of the left ventricle. The pulmonary artery and its branches were conspicuous by their absence. This was more marked on the last examination.

The patient was placed in an oxygen tent was given penicillin and local treatment to the burn. He did well until October 2, 1950 when the patient's temperature dropped to 96.0 F., but this improved when blankets and hot water bottles were applied. The following morning he was noted to be

listless and unresponsive. He had a very dusky color. The respirations were very labored (about 60 per minute). The liver edge was just palpable. There was no movement in the extremities. The patient vomited some brownish material through his nose and mouth. He was given one-half milliliter of coramine, one-half milliliter of adrenalin and artificial respiration was performed. The infant failed to respond and death occurred at 8:45 A.M. thirteen days after the original admission.

DISCUSSION

John A. Washington, M.D.: The significant features in this case seem to be as follows:

Cyanosis since birth.

Death at seven months.

Murmur not striking.

Heart little if any enlarged.

A boot-shaped heart seen on x-ray indicating the absence of the pulmonary artery or a very small pulmonary artery.

Left ventricular preponderance as indicated by electrocardiogram.

6,400,000 red blood cells and 16 grams of hemoglobin.

The transient, unilateral, convulsive movements which occurred when the baby was extremely cyanotic must be mentioned in passing. Presumably, these were caused by anoxia although convulsions are not characteristic of central nervous system anoxia. The classical accident to the brain in a cyanotic child is thrombosis of cerebral vessels resulting from polycythemia. There is nothing transient about the effects of thrombosis however. Certainly this baby's primary trouble was in the heart.

The combination of cyanosis and the boot-shaped silhouette by x-ray brings to mind first the tetralogy of Fallot. Of the four abnormalities found in this condition the first to be mentioned is *stenosis of the pulmonary artery*. Blood entering the right side of the heart from the vena cava passes through the right auricle to the right ventricle normally. The bulk of it is unable to proceed on to the lungs because the pulmonary artery is stenosed. Well, where does it go? It passes into a *defect in the ventricular septum* It does not get all the way to the left ventricle, however, because the *entrance to the aorta sets just over the defect in the septum*. Hence, the unoxygenated blood passes directly into the aorta and so on to the systemic circulation. The little amount of blood which reaches the lungs via the stenosed pulmonary artery reaches the aorta by the usual route through the left side of the heart. The left side of the heart is thus underworked, and *the right ventricle hypertrophies* because it does most of the pumping. In our case this fourth requisite for diagnosing the tetralogy of Fallot is lacking. The

electrocardiogram shows, instead, left ventricular preponderance and fluoroscopic examination is said to have confirmed this.

Taussig states that in cyanotic infants the only malformation which gives left ventricular hypertrophy is *underdevelopment or absence of the right ventricle with tricuspid and pulmonary atresia.* In this condition blood entering the right auricle finds no exit into the right ventricle through the tricuspid valve which is either atretic or extremely hypoplastic. The blood instead passes through a defect in the auricular septum or through the foramen ovale to the left auricle, thence to the left ventricle and so to the aorta, bypassing the lungs completely. Life is sustained by the patency of the ductus arteriosus which carries some blood from the aorta back to the pulmonary artery distal to its atretic portion. Such infants usually die in a few months, but may survive longer depending, to a great extent, on the continued patency of the ductus. Taussig mentions several variations of this condition. These are:

1. Tricuspid atresia and ventricular septal defect combined with extreme stenosis of the infundibulum of the right ventricle. Infants with this set-up usually live beyond the age of two years.

2. Complete transposition of the great vessels combined with aortic atresia in combination with a non-functioning right ventricle. The duration of life here is brief.

3. Extreme dextro-position of the aorta combined with pulmonary atresia in combination with a defective right ventricle. The duration of life in this instance is brief also.

4. Complete transposition of the great vessels and tricuspid atresia. During the first month of life the contour of the heart may resemble that of a non-functioning right ventricle.

Although these last four conditions cannot be ruled out, the most likely diagnosis is underdevelopment of the right ventricle with tricuspid and pulmonary atresios. Before closing it should be mentioned that this condition might be helped by the Taussig-Blalock operation which would augment the shunt of unoxygenated blood from the aorta to the pulmonary artery and, in case the ductus closed, would substitute for it.

PATHOLOGIC DISCUSSION

Sanford Leikin, M.D.: The body was that of a well developed and well nourished white male measuring 66 centimeters and weighing 6 kilograms. There was a desquamated area over the right thigh, measuring 5 x 3.5 centimeters.

The prominent findings were in the heart. The cardiac borders extended 3 centimeters to the right of the midline and 5 centimeters to the left. The heart weighed 102 grams (normal—31 grams). The great veins and coronary

sinus entered the right auricle in normal relationship. The foramen ovale was patent and measured 6 millimeters in diameter. The tricuspid valve, the right ventricle, and pulmonary valve were the primary sites of the pathology. The tricuspid valve was atretic and measured 6 millimeters in diameter across its base. There was only a small right ventricle which contained no blood.

The pulmonary venous return was normal. The wall of the left ventricle measured 8 millimeters in thickness. The pulmonary artery was hypoplastic and measured 4 millimeters in diameter. On tracing this artery back to its source it was found that the pulmonary valve was atretic and measured 0.2 millimeters. The pulmonary artery arose in the heart musculature just to the right of the base of the aorta and did not communicate with either ventricle. The ductus arteriosus was patent but at its narrowest point was only 1 millimeter in diameter.

There was a moderate amount of thick, yellow mucopurulent material which filled the trachea and large bronchus. Both lungs were pink and crepitant. A moderate amount of frothy, bloody material exuded from the compressed cut surface.

The liver weighed 236 grams (normal 200 grams). It was bluish-red and the serosal surface was smooth. On cut section the normal architecture was obliterated and the surface was pale yellow. The blood vessels were engorged with blood. The gall bladder and bile ducts were normal.

The spleen was dark red, firm and weighed 25 grams (normal 16 grams). The capsule was slightly roughened by small white fibrotic areas which measured 2 to 7 millimeters. The organ cut with increased resistance. On cut section, the white fibrotic areas extended into the splenic pulp and produced a slightly roughened surface. The malphigian bodies were somewhat indistinct.

The gastro-intestinal tract, pancreas, and adrenals were normal.

The kidneys were bluish pink and cut section revealed the vessels to be engorged. The cortices were bluish brown and the medullae were bluish.

On opening the cranial cavity the vessels over the arachnoid and cortex were markedly dilated and engorged with dark red blood. The brain was firm. There was some irregularity in the size of the gyri of both hemispheres. There was greater disproportion on the left than on the right. On coronal section, the brain was dusky and the ventricular system was collapsed. There was no evidence of infarction.

Microscopic Examinations:

Sections taken from the left ventricle of the heart showed no pathologic changes. Some of the pulmonary alveoli contained macrophages and a few were collapsed. The bronchi were filled with eosinophilic debris.

The spleen showed marked evidence of chronic passive congestion in that

the trabeculae were increased in size, the malphigian bodies and germinal centers were reduced in size and there was an increase in the number of fibrous connective tissue strands. Between the strands of connective tissue there were a few red blood cells, many fibroblasts, macrophages, and lymphocytes. Many of the smaller blood vessels were thickened and fragmented. The sinusoids of the liver were dilated and many of the hepatic cells contained large vacuoles.

On examination of the brain there was some thickening of the meninges and a moderate amount of extravasation of blood was noted in the subarachnoid space.

The remaining organs were normal on microscopic examination.

The pathologic diagnosis was:

1. Atresia of the tricuspid valve.
2. Non-functioning right ventricle.
3. Atresia of the pulmonary valve.
4. Hypoplastic pulmonary artery.
5. Patent foramen ovale.
6. Patent ductus arteriosus.
7. Chronic passive congestion of the viscera.

Clinically, this child showed a marked cyanosis, attacks of cerebral anoxia, left heart enlargement, a mild polycythemia with decreased pulmonary blood flow. The atypical features were the absence of a pure second sound and lack of liver pulsation.

The only way for blood to reach the lungs by way of the patent foramen ovale was through the left auricle and ventricle and then out through the aorta, and then through the patent ductus arteriosus to the pulmonary arteries. The death of this patient was probably due to the slow closure of the ductus arteriosus. The ductus arteriosus was very small in this case and probably was responsible for the cerebral anoxia which was produced. This caused the patient's death. This is the usual course in this activity.

INTRAMUSCULAR ADMINISTRATION OF CHLORAMPHENICOL
A PRELIMINARY NOTE

Special Report No. 198

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Chloramphenicol, a neutral white crystalline substance in pure form, is minimally soluble in water or normal saline. The drug possesses neither acidic nor basic groups capable of forming salts soluble in aqueous media. A solution containing 15 per cent chloramphenicol can be prepared in propylene glycol but injection of this solution intramuscularly in doses of .5 to 1.0 grams causes considerable local tissue induration, extensive edema, hemorrhage, and necrosis.[1]

Recently a microcrystalline-powdered form of chloramphenicol has been made available for experimental purposes by Parke, Davis Company.[2] When 4 to 5 milliliters of normal saline or distilled water is added to 1 gram of this material, a suspension is formed which can be readily taken up and injected through a 20 or 21 gauge needle.

At Children's Hospital, three infants ranging in age from two months to seven months were given 1 gram of microcrystalline chloramphenicol in saline intramuscularly and venous blood was obtained for chloramphenicol assays at intervals of 3, 6, 12, 24, 48, 72, and 96 hours.

Table I indicates the nature of the blood levels which were obtained. As will be noted, a dose of 1 gram intramuscularly in patients #1 and #2 (amounting to 150 milligrams per kilogram) produced excellent chloramphenicol blood levels during the first 24 hours ranging from 10.7 to 29.2 micrograms per milliliter. Highest blood titers were reached after 6 to 12 hours while adequate therapeutic levels were still demonstrable after 24 hours. Sub-therapeutic or trace levels were observed by 48 hours and thereafter. In patient #3, an infant weighing 3.5 kilograms, a dose of 1 gram (300 milligrams per kilogram) produced extremely high blood levels ranging between 34.5 to 77 micrograms per milliliter during the first 24 hours while an adequate therapeutic titer was still present after 72 hours.

Seven other children ranging in age from two months to two years were given 1 gram of chloramphenicol suspension intramuscularly and in all instances, an adequate therapeutic titer was still demonstrable after 24 hours.

No local or systemic reactions were observed in any of the ten patients in this study.

COMMENT

Preliminary investigations would suggest that the intramuscular injection of a microcrystalline suspension of chloramphenicol is a feasible mode of administration of the drug. In infants ranging in weight from 3 to 12 kilograms, adequate blood levels lasting for at least 24 hours can be obtained with a daily dose of 1 gram of the drug.

In view of the frequent difficulties attendent to the oral administration of chloramphenicol in the pediatric age group, the demonstration that the drug can be given intramuscularly without any local tissue reaction assumes an aspect of some practical importance.

Further experiments are currently being carried out to determine the optimal dose of the drug in different age groups.

TABLE I

PATIENT	WEIGHT (KGMS)	DOSE OF I. M. CHLORAMPHENICOL	CHLORAMPHENICOL BLOOD LEVELS (MCGMS./CC.)						
			3 hrs.	6 hrs.	12 hrs.	24 hrs.	48 hrs.	72 hrs.	96 hrs.
1	6.5	1 gm. (150 mgm/kgm)	20.8	24.2	29.2	15.8	3.9	0	1.1
2	6.4	1 gm. (150 mgm/kgm)	16.2	24.0	20.4	10.7	0	1.6	0
3	3.5	1 gm. (300 mgm/kgm)	34.5	37.8	50.1	77.0	33.2	18.9	0

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